EXHIBIT 1

D48

T0055/10-3302

European Patent No. 1 264 597 in the name of The Children's Medical Center Corporation

DECLARATION OF DR GARETH MORGAN

I, Gareth Morgan, Professor of Haemato-Oncology, The Institute of Cancer Research, UK, do declare and state that:

1. A copy of my CV is attached as Exhibit 1 to this declaration, which gives full details of my career to date. I am currently the Head of the Department of Haematology at the Royal Marsden Hospital in London, which is the largest Oncology hospital in Europe. As will be evident, I have been a cancer specialist for over 25 years.

2. I have been asked, by the exclusive licensee of EP 1,264,597, Celgene Corporation, to provide my expert opinion in connection with this patent. I am presently, and have been in the past, a paid consultant for Celgene Corporation with respect to a variety of matters.

3. I have read and am fully familiar with the invention described in EP 1,264,597. I understand that it relates to the use of thalidomide in the treatment of various oncogenic diseases.

4. Claim 1 of EP 1,264,597 defines the use of thalidomide "for the treatment of solid and blood-borne tumours". It is my opinion that reference to "the treatment of solid and blood-borne tumours" refers to the direct treatment of a tumour *per se*.

5. In oncological terms, treatment of a tumour is a reduction in the size of that tumour. In modern terminology, this is brought about by inducing

apoptosis of the tumour cells with the aim of obtaining a complete response. There are multiple different response criteria for different tumour sub-types. Generally, however, these all rely on reduction in the size of the tumour. For non-solid tumours or blood borne-tumours, where there is a leukaemic phase with a high white blood cell count, the reduction in size of the tumour would amount to a reduction in the white cell count, and infiltration of the bone marrow.

6. Therefore, in the context of the statement used in claim 1 of EP 1,264,597, the contention would be that thalidomide should be used for the reduction in size or bulk of the tumour cell.

7. There is no implication in the statement used in claim 1 that thalidomide should be used for improving the well-being of the patient. Indeed, thalidomide was a known sedative, and if patients were not sleeping prior to the institution of treatment then it would not be at all surprising if they were to improve their ability to sleep.

8. An oncologist would not consider palliation and direct treatment of the tumour in the same phrase. Palliation relates to a subjective improvement in the well-being of the patient. Palliation can be improved by reducing pain, reducing nausea, reducing a temperature, and while, if there is a reduction in the tumour bulk, it can sometimes be associated with palliative effects for the patient, treatment can often impair palliation by increasing side effects. Thus, the two concepts are totally separate.

9. I have also read and am fully familiar with the paper cited in the opposition proceedings of EP 1,264,597, i.e. Olsen *et al.*, Clinical Pharmacology and Therapeutics, 1965, Vol. 6, No.3, pp. 292-297 (D1).

10. The design of the study described in D1 was entirely flawed. There were 21 patients treated for 14 different types of tumour, and the study was not blinded. The study was open label with no randomisation, with patients

selected from the clinic, who were then subsequently treated with thalidomide. This is an inadequate design to assess tumour response. In 1965, CT scans were generally not available, and response to treatment and/or stable disease would have been judged by palpation and measuring the tumours. For example, intra-abdominal masses and lymph nodes would have been measured with callipers or a tape measure.

11. Although the Opposition Division stated that 2 out of 21 patients exhibited objective improvement, I would say that D1 in fact showed no efficacy whatsoever for patients with any of the malignancies. There is nothing in D1 that would lead me to conclude that any patient had improved at all. There was no data disclosed whatsoever that would lead a Clinician to suspect that the drug was useful, and to use it in further cancer patients. Nor would anything in D1's report lead a Clinician to treat any particular tumour patient with this drug with the aim of obtaining a direct response on tumour size.

12. All that was reported in D1 was improved sedation, which would have been expected because thalidomide was a known sedative drug. Sedation simply refers to it being a sleeping tablet.

13. Subjective improvement and subjective benefit is not a credible end-point for a drug evaluation study. Even for a drug that is inactive, the placebo effect of having attention paid to a patient's condition by an oncologist can lead to a subjective improvement. It seems likely that the patients were actually better sedated because they knew they were receiving a sedative drug. Subjective well-being, subjective improvement and subjective benefit do not have any implications for a mode of action directly against the tumour itself.

14. The ARA-C corneal assay for angiogenesis that is described in EP 1,264,597 is well described. It is fully controllable, and changes in this model can be readily measured. It is also possible to repeat the

experiment on numerous occasions, as the inventor has done, so that even small changes that are present can be confirmed as being statistically relevant. Thus, the statistical confidence limits around thalidomide's ability to inhibit angiogenesis are well described in EP 1,264,597. In contrast, the design of the study described in D1, which looks at clinical responses, was so poorly designed that the application of any form of statistics to it would be flawed.

15. In 1965, CT scanning was generally not available. Clinical assessments would have been measured in terms of change in tumour size by physical examination of the patient, and, in the case of multiple myeloma, a reduction in the level of paraprotein and decrease in marrow infiltration with plasma cells. These are effective clinically controlled measures of disease response. However, D1, given it's highly flawed methodology, did not demonstrate a positive response in any patient.

16. In 1965, there was a paucity of novel agents. Thus, if any of the cases treated in D1 had responded to thalidomide, or there was any evidence of objective improvements in any tumour specific variable, then it is likely that there would have been widespread uptake of the drug by oncologists. There was no such evidence of response, and so the drug was not widely used by Clinicians. The only use of thalidomide from that time was in the treatment of graft versus host disease and erythema nodosum leprosum. I am not aware of any publications of cancer studies at that time that followed on from D1.

17. I note that the opponent argued that it is not the lack of anti-tumour effects that meant that thalidomide was not widely taken up, but rather that it was because it was known to be teratogenic, which deterred Clinicians. This is clearly not true. After all, Olsen *et al.* themselves took it up, and administered it to patients in their trial soon after it's teratogenic effects had been discovered.

18. The use of radiotherapy for treating cancer patients is widespread despite the risks it presents to foetuses. Indeed, the same is true for all chemotherapy drugs, and even some differentiation therapies such as retinoic acid vitamin E analogues. The use of all of these agents is widespread, and there has not been any effective risk management system in place for these drugs. Following the introduction of thalidomide, because of its history, an effective risk management was developed, but this has not been widely used outside the use of thalidomide. I believe that if thalidomide had been shown to be an effective anti-cancer drug, it would have been widely taken up by Clinicians.

19. It is my belief that a skilled Oncologist reading D1 in 1965 would have concluded that thalidomide was a known sedative and anti-emetic drug. It was known to cause phocomelia, and to be teratogenic to foetuses *in vivo*. I do not understand the logic of even how it was considered reasonable to treat 21 patients with a drug that had no evidence of anti-cancer benefit. Despite this, it was given to these 21 patients. None of them showed objective evidence of any improvement in their malignancy, and the obvious conclusion would have been that it was ineffective as an anti-cancer drug. It could only have been reasonable to conclude that it was an effective sedative.

20. I hereby declare that all statements made herein of my own knowledge are true.

Declarant:  .....

DR GARETH MORGAN

Date: 19th March 2010.....

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